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Structural Analogues of 5-OMe-BPAT: Synthesis and Interactions with Dopamine D_2, D_3, and Serotonin 5-HT_{1A} Receptors

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Abstract—Several structural analogues of 5-methoxy-2-[*N*-(2-benzamidoethyl)-*N*-*n*-propylamino]tetralin (5-OMe-BPAT, **1**), a representative of a series of 2-aminotetralin-derived benzamides with potential atypical antipsychotic properties, were synthesized and evaluated for their ability to bind to dopamine D_{2A}, D_3, and serotonin 5-HT_{1A} receptors in vitro. The structure–affinity relationships revealed that the aromatic ring of the benzamide moiety of **1** contributes to the high affinities for all three receptor subtypes. Furthermore, **1** may interact with the dopamine D_2 and D_3 receptors through hydrogen bond formation with its carbonyl group. Investigation of the role of the amide hydrogen atom by amide *N*-alkylation was not conclusive, since conformational aspects may be responsible for the decreased dopaminergic affinities of the *N*′-alkylated analogues of **1**. The effects of the amide modifications on the serotonin 5-HT_{1A} receptor affinity were less pronounced, suggesting that the benzamidoethyl side-chain of **1** as a whole enhances the affinity for this receptor subtype probably through hydrophobic interactions with an accessory binding site. The structural requirements for the substituents at the basic nitrogen atom supported the hypothesis that the 2-aminotetralin moieties of the 2-aminotetralin-derived substituted benzamides may share the same binding sites as the 2-(*N*,*N*-di-*n*-propylamino)tetralins.

Introduction

2-Aminotetralin-derived substituted benzamides comprise a series of compounds with mixed dopamine D_2, D_3, and serotonin 5-HT_{1A} receptor binding properties.[1] The lead compound of this series, 5-methoxy-2-[N-(2-benzamidoethyl)-N-*n*-propylamino]tetralin (5-OMe-BPAT, **1**, Chart 1) has nanomolar affinities for all three receptor subtypes. The enantiomers of **1** were shown to possess different pharmacological properties:[2] whereas both enantiomers turned out to be full serotonin 5-HT_{1A} receptor agonists in vitro, they showed different intrinsic efficacies at dopamine D_2 receptors in vivo: (*S*)-**1** had dopamine D_2 receptor-stimulating properties, while (*R*)-**1** behaved as a dopamine D_2 receptor antagonist. Since both enantiomers were devoid of cataleptogenic activity, and showed low affinities for a number of other relevant receptor subtypes, they comprise interesting compounds for further exploring the dopamine D_2/serotonin 5-HT_{1A} hypothesis of atypical antipsychotic drug action.[3–6] Previously reported structure–affinity relationships (SAFIRs)[1] indicated that the benzene ring of the benzamide moiety of **1** can be replaced by small aromatic isosters, while attachment of substituents to this ring generally leads to somewhat lower affinities. Furthermore, the benzamidoethyl side-chain appears to enhance the affinities for both the dopaminergic and serotonin 5-HT_{1A} receptors, and thus may occupy an accessory binding site in all three receptor subtypes. In addition, the SAFIRs suggested that the aminotetralin parts of the molecules probably occupy the same binding sites as the corresponding 2-(*N*,*N*-di-*n*-propylamino)tetralins (DPATs). In order to shed more light on the importance of the various functional groups as present in the 2-aminotetralin-derived benzamides, and hence on the mode of binding of these compounds to the receptors, various structural analogues of **1** were synthesized and evaluated for their ability to bind to dopamine D_{2A}, D_3, and serotonin 5-HT_{1A} receptors in vitro.

Key words: Dopamine; serotonin; 2-aminotetralin; structure–affinity relationships.

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Chemistry

In order to investigate whether an aromatic ring attached to the amide carbonyl moiety is required for

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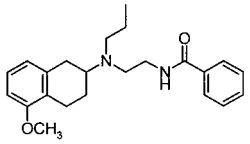

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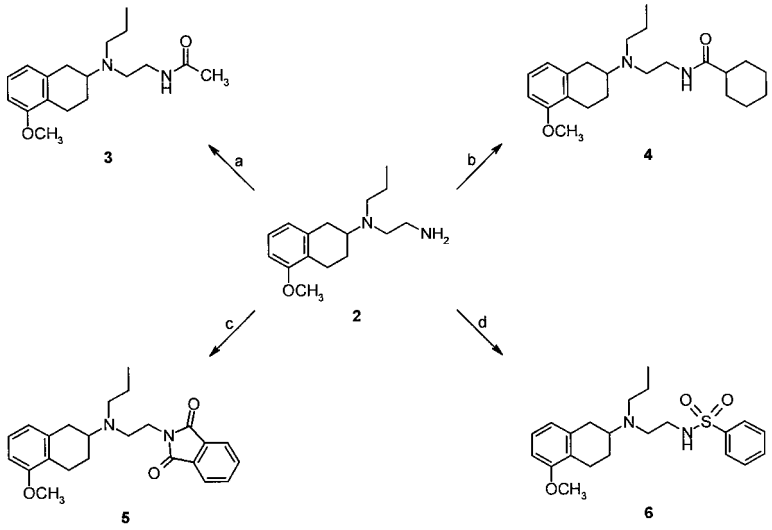
Chart 1.

high affinity, the acetamido and the cyclohexylcarboxamido analogues of **1** were synthesized (Scheme 1). 5-Methoxy-2-[*N*-(2-aminoethyl)-*N*-*n*-propylamino]tetralin (**2**)[1] served as starting material for both amides: reaction with acetic anhydride in the biphasic medium water/ethyl acetate, using sodium acetate as a base, gave the acetamide **3**, while reaction with cyclohexylcarboxylic acid chloride in the biphasic medium sodium hydroxide/dichloromethane yielded the cyclohexylcarboxamide **4**.[7]

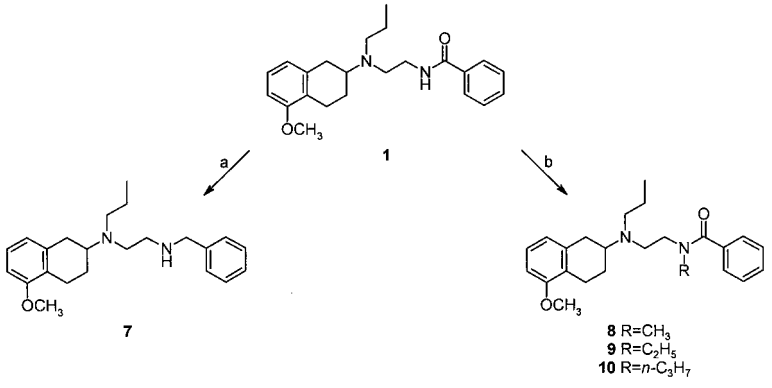
Also starting from **2**, two analogues of **1** with different benzamide isosters were prepared (Scheme 1). The phthalimido analogue **5** was prepared by allowing **2** to react with phthalic anhydride in boiling glacial acetic acid, while reaction of **2** with benzenesulfonyl chloride in the biphasic medium water/chloroform, using potassium carbonate as a base, gave the benzenesulfonamido analogue **6**.

Reduction of the carbonyl group of **1** with $LiAlH_4$ in boiling THF gave the *N*′-benzyl analogue **7** (Scheme 2). Selective alkylation of the amide nitrogen of **1** with the appropriate alkyl iodide, employing dimethyl sulfoxide as a solvent and solid potassium hydroxide as a base,[8] gave the *N*′-methyl-, *N*′-ethyl- and *N*′-*n*-propyl analogues **8**, **9**, and **10**, respectively. Compounds **5–10** should reveal whether the presence of a secondary amide functionality, capable of forming hydrogen bonds with both its carbonyl oxygen and N−H hydrogen atom, is essential for high affinities at the receptors.

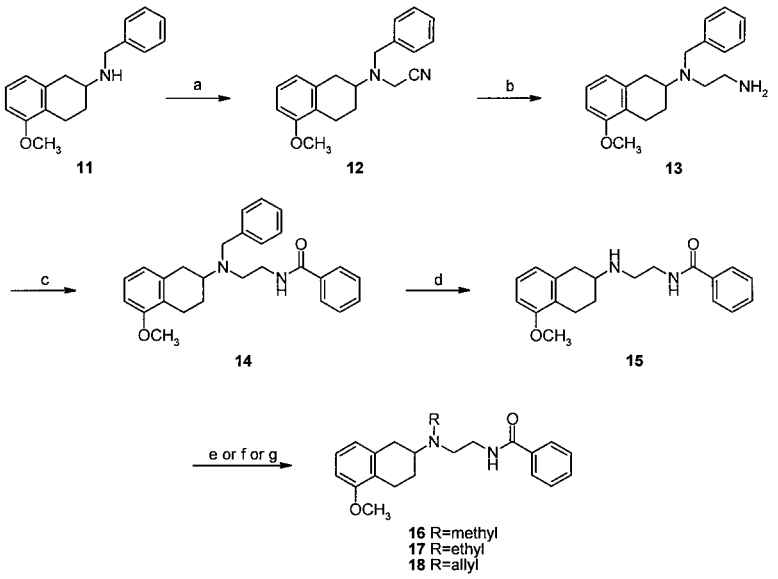
In order to investigate the structural requirements for the nitrogen substituent next to the benzamidoethyl side-chain, the *N*-benzyl, hydrogen, *N*-methyl, *N*-ethyl, and *N*-allyl analogues of **1** were prepared. The synthesis of these compounds is outlined in Scheme 3. *N*-Alkylation of 5-methoxy-2-(*N*-benzylamino)tetralin (**11**)[9] with bromoacetonitrile in boiling acetone, using potassium carbonate as a base and potassium iodide as a catalyst, gave the *N*-cyanomethyl intermediate **12**, which was reduced with $LiAlH_4$ in boiling THF to the corresponding



Scheme 1. *Reagents and conditions*: (a) Ac_2O, NaOAc, EtOAc, H_2O, rt; (b) $C_6H_{11}COCl$, 10% NaOH, CH_2Cl_2, rt; (c) phthalic anhydride, NaOAc, AcOH, Δ; (d) $C_6H_5SO_2Cl$, K_2CO_3, $CHCl_3$, H_2O, rt.



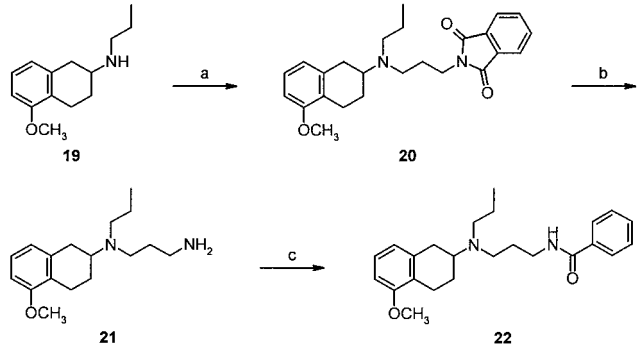
Scheme 2. *Reagents and conditions*: (a) $LiAlH_4$, THF, Δ; (b) RI, KOH, DMSO, rt.



Scheme 3. *Reagents and conditions*: (a) $BrCH_2CN$, K_2CO_3, KI, acetone, Δ; (b) $LiAlH_4$, THF, Δ; (c) C_6H_5COCl, 10% NaOH, CH_2Cl_2, rt; (d) Pd/C (10%), H_2, EtOH, rt; (e) formaldehyde, Pd/C (10%), H_2, MeOH, Δ; (f) acetaldehyde, Pd/C (10%), H_2, EtOH, Δ; (g) CH_2CHCH_2Br, Cs_2CO_3, KI, MeCN, Δ.

primary amine **13**. Amide formation with benzoyl chloride as described for **4** yielded **14**, the *N*-benzyl analogue of **1**. Catalytic debenzylation of **14** by hydrogenation gave **15**, the N−H analogue of **1**, which served as a starting point for the preparation of the *N*-methyl, *N*-ethyl and *N*-allyl analogues, **16**, **17**, and **18**, respectively. Thus, reductive amination of the appropriate aldehydes with **15** and hydrogen, employing ethanol as a solvent and Pd/C (10%) as a catalyst, gave **16** and **17**, while *N*-alkylation of **15** with allyl bromide in boiling acetonitrile, employing cesium carbonate as a base and potassium iodide as a catalyst, yielded **18**.

Finally, a chain-elongated analogue of **1** was prepared, as outlined in Scheme 4. 5-Methoxy-2-(*N*-*n*-propylamino)-tetralin[10] (**19**) was *N*-alkylated with *N*-(3-bromopropyl)-phthalimide in boiling acetonitrile, employing cesium carbonate as a base and potassium iodide as a catalyst. The resulting phthalimide **20** was hydrolyzed to the corresponding primary amine **21** with hydrazine in ethanol. Amide formation with benzoyl chloride, as described for **4**, resulted in the *N*-(3-benzamidopropyl) analogue **22**.



Scheme 4. *Reagents and conditions*: (a) N-(3-bromopropyl)phthalimide, K_2CO_3, KI, acetone, Δ; (b) hydrazine hydrate, EtOH, rt; (c) C_6H_5COCl, 10% NaOH, CH_2Cl_2, rt.

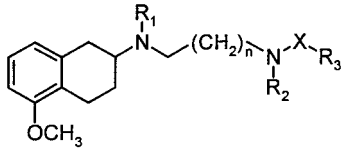
Pharmacology

Compounds **3–15** were evaluated for their ability to compete for [^{3}H]-raclopride binding to cloned human dopamine D_{2A} receptors (expressed in Ltk$^-$ cells) and cloned human dopamine D_3 receptors (expressed in CHO cells), and their ability to compete for [^{3}H]-8-OH-DPAT binding to rat hippocampal membranes containing serotonin 5-HT_{1A} receptors in vitro. The results of these binding studies are shown in Table 1. For comparison purposes, the previously reported affinities of **1**, haloperidol, and clozapine have been included.[1]

Results and Discussion

5-Methoxy-2-[*N*-(2-benzamidoethyl)-*N*-*n*-propylamino]-tetralin (5-OMe-BPAT, **1**) is one of the most potent representatives of a series of compounds with mixed dopamine D_2, D_3, and serotonin 5-HT_{1A} receptor binding properties. Previous SAFIR studies on the series have shown that the aromatic nucleus of the benzamide moiety of **1** can be replaced by small aromatic isosters, including 2-thiophene and 3-thiophene, without serious loss of affinity for the indicated receptor subtypes.[1] Replacement of this ring by 1-naphthalene or 2-naphthalene, however, resulted in about 6- and 20-fold lower affinities for dopamine D_{2A} and serotonin 5-HT_{1A} receptors, respectively. The results in Table 1 show that replacement of the benzamide moiety by an acetamide group (**3**) strongly decreases the affinities for both the dopamine D_{2A} and serotonin 5-HT_{1A} receptor. Replacement of the benzene ring by a cyclohexyl ring (**4**), however, even enhances the affinities for these two receptor subtypes. Apparently, a lipophilic substituent with about the size of a phenyl ring, but not necessarily aromatic in nature, is optimal for high affinities for both the dopamine D_{2A} and serotonin 5-HT_{1A} receptor.

Table 1. Receptor binding of compounds **1**, **3–10**, **14–18**, **20**, **22**, haloperidol, and clozapine



						K_i (nM)[a]		
Compd	R_1	R_2	R_3	X	n	D_{2A}	D_3	5-HT_{1A}
1	*n*-propyl	H	Phenyl	C=O	1	3.2 ± 0.2	0.58 ± 0.05	0.82 ± 0.11
3	*n*-propyl	H	Methyl	C=O	1	150 ± 60	ND[b]	123 ± 9
4	*n*-propyl	H	Cyclohexyl	C=O	1	2.2 ± 0.1	0.73 ± 0.26	< 0.5
5	*n*-propyl		Phthalimide[c]		1	> 1000	> 1000	> 1000
6	*n*-propyl	H	Phenyl	SO_2	1	46.3 ± 7.0	20.5 ± 1.5	1.7 ± 0.3
7	*n*-propyl	H	Phenyl	CH_2	1	16.2 ± 10	ND	1.8 ± 0.3
8	*n*-propyl	Methyl	Phenyl	C=O	1	208 ± 22	51.6 ± 3.2	20.2 ± 0.7
9	*n*-propyl	Ethyl	Phenyl	C=O	1	316 ± 177	ND	17.9 ± 1.9
10	*n*-propyl	*n*-propyl	Phenyl	C=O	1	260 ± 61	ND	4.6 ± 0.6
14	Benzyl	H	Phenyl	C=O	1	264 ± 3	ND	223 ± 11
15	H	H	Phenyl	C=O	1	8.7 ± 0.3	8.9 ± 2.5	4.1 ± 0.9
16	Methyl	H	Phenyl	C=O	1	11.7[d]	ND	45.7[e]
17	Ethyl	H	Phenyl	C=O	1	2.9 ± 1.1	3.2 ± 0.3	0.65 ± 0.20
18	Allyl	H	Phenyl	C=O	1	9.1 ± 1.1	2.3 ± 0.1	0.28 ± 0.05
20	*n*-propyl		Phthalimide[c]		2	20.5 ± 0.7	3.3 ± 0.2	14.9 ± 0.4
22	*n*-propyl	H	Phenyl		2	46.3 ± 6.3	ND	15.9 ± 4.0
Hal[f]	—	—	—	—	—	0.67 ± 0.11	2.7 ± 0.6	2213 ± 585
Cloz[g]	—	—	—	—	—	59.8 ± 7.8	83.3 ± 9.9	304 ± 184

[a]Mean values ± s.e.m. of 2–4 independent experiments, unless otherwise indicated.
[b]ND: not determined.
[c]R_2-N-X-R_3 = phthalimide.
[d][^{3}H]-spiperone binding, rat striatum, $n = 1$.
[e]Rat frontal cortex, $n = 1$.
[f]Hal: haloperidol.
[g]Cloz: clozapine.

The phthalimidoethyl analogue **5** showed no affinity for the receptors under investigation. Apparently, the presence of the additional carbonyl group in the phthalimide moiety prohibits binding to the receptors. This could be caused by steric or electronic factors, or a combination of both. Replacement of the carbonyl group of **1** by a SO_2 group results in about 15-fold, 35-fold, and 2-fold loss of affinity for the dopamine D_{2A}, D_3, and serotonin 5-HT_{1A} receptor, respectively (cf. **6**). Reduction of the carbonyl group to a methylene group (cf. **7**) reduces the affinity for the dopamine D_{2A} receptor about 5-fold and the affinity for the serotonin 5-HT_{1A} receptor about 2-fold. These results suggest that the presence of a single carbonyl group, as in the benzamide moiety, is beneficial for high dopaminergic receptor affinity, but not for binding to serotonin 5-HT_{1A} receptors. Therefore, the carbonyl group of **1** may act as a hydrogen bond acceptor when this compound binds to dopamine D_{2A} and D_3 receptors. Although the SO_2 group of **6** can also act as a hydrogen bond acceptor, the directionality of the SO groups apparently is not optimal for hydrogen bond formation. One of the SO groups may be orientated in a coplanar fashion with the benzene ring, mimicking the carbonyl group of **1**, but the trigonal bipyramidal configuration of the SO_2 moiety then dictates the other SO group to be directed in an orientation almost perpendicular to the plane of the benzene ring, and pointing in the same direction as the amide hydrogen. This phenomenon could account for the lower affinities of **6** at the dopaminergic receptors than **1**.

Alkylation of the benzamide nitrogen atom resulted in a strong decrease predominantly in dopaminergic affinity: compounds **8–10** all have low affinities for the dopamine D_{2A} receptor. In addition, the affinity of **8** for the dopamine D_3 receptor, compared to **1**, is also reduced. However, the affinities of **8–10** for the serotonin 5-HT_{1A} receptor are still considerable. Moreover, elongation of the *N*′-alkyl substituent, going from methyl (**8**) via ethyl (**9**) to *n*-propyl (**10**), even seems to restore most of the serotonergic activity, suggesting that the *N*′-*n*-propyl group may reach an accessory binding site in the serotonin 5-HT_{1A} receptor. At first sight, these observations suggest that the diminished affinities of compounds **8–10** for the dopamine D_{2A} receptors are caused either by steric hindrance of the *N*′-alkyl groups with one or more amino acid residues in the binding site, or by preventing the formation of a hydrogen bond with a hydrogen bond accepting amino acid residue in the binding site. This latter hypothesis would also explain the lack of affinity for the dopamine D_{2A} receptor of the phthalimide analogue **5**, where the presence of the additional carbonyl oxygen atom would cause strong repulsive interactions with the hydrogen bond acceptor atom of the receptor.

However, differences in conformational behaviour of the benzamide moieties of **8–10** and **1** may also account for the observed results. ^{1}H and ^{13}C NMR spectra of **8–10**, taken at room temperature and using deuterated chloroform as the solvent, indicated the presence of two

stable conformers in a 1 to 1 ratio. Dynamic NMR experiments, performed on **8–10** in deuterated DMSO, deuterated toluene, and deuterated tetrachloroethane, showed coalescense of the resonances upon heating, the coalescence temperature being dependent on the solvent. After cooling to room temperature, the spectra again indicated the presence of two stable conformers in a 1 to 1 ratio. Since these observations suggested that the rotation behaviour of the amide bonds in **8–10** might be responsible for the coexistence of two stable conformers at room temperature, molecular modeling studies were undertaken to rationalize this phenomenon. Thus, in order to determine the rotation barrier and the locations of the energy minima for the amide bonds of **1** and **8–10** *N*-methylbenzamide and *N*,*N*-dimethylbenzamide were taken as model compounds for **1** and **8**, respectively, and the energies of all rotamers, obtained by rotating the amide torsion angle with a resolution of 10°, were calculated semi-empirically using the AM1 method.[11] The results of these calculations are shown in Figure 1. Rotation of the torsion angle $\tau_{1\text{-}2\text{-}3\text{-}4}$ of *N*-methylbenzamide, as defined in Figure 1, revealed three minimum energy rotamers, at $\tau = 30°$ ($\Delta E = 9.3$ kcal/mol), $\tau = 180°$ ($\Delta E = 0.0$ kcal/mol), and $\tau = 350°$ ($\Delta E = 13.2$ kcal/mol), and one saddle-point, at $\tau = 270°$ ($\Delta E = 21.3$ kcal/mol), respectively. At $\tau = 180°$ the amide moiety adopts the more stable *trans* orientation, while at $\tau = 30°$ and $\tau = 350°$ it adopts the less likely *cis* orientation. When entropy and solvent effects are neglected, the Boltzmann equation predicts that the populations of the minima at $\tau = 30°$ and $\tau = 350°$ can be neglected. In other words, *N*-methylbenzamide will exclusively adopt the minimum energy conformation at $\tau = 180°$. Therefore, it can be assumed that the amide moiety of **1** will also exclusively adopt the *trans* orientation, which is supported by the NMR spectra reflecting a single rotamer.

Two minimum energy rotamers were observed upon stepwise rotation of $\tau_{1\text{-}2\text{-}3\text{-}4}$ in *N*,*N*-dimethylbenzamide. These minima occurred at $\tau = 0°$ and $\tau = 180°$, corresponding to the *cis* and *trans* orientation of the amide moiety, respectively. In the *cis* conformer, the two *N*-methyl substituents, as defined in Figure 1, have exchanged positions. Since both rotamers have equal ΔE values, they are predicted to be populated in a 1 to 1 ratio at room temperature. The rotational barriers at $\tau = 90°$ [$\Delta(\Delta E) = 13.4$ kcal/mol] and $\tau = 280°$ [$\Delta(\Delta E) = 13.6$ kcal/mol] have to be surmounted in order to allow for isomerization of the two minimum energy rotamers. It is likely that this is also the case for compounds **8–10**, where the presence of both the *cis* and the *trans* form of the amides in a 1 to 1 ratio accounts for the double resonances observed in the NMR spectra of these compounds at room temperature. Upon sufficient heating, the rotation barriers can be overcome and the *cis* and *trans* forms may isomerize, which is reflected by the coalescence of their resonances in the NMR spectra. Importantly, these observations suggest that the two forms may also exist under biological conditions. It can therefore not be excluded that the *cis* amides of **8–10** have different pharmacological properties than the *trans* rotamers, which complicates the interpretation of the receptor binding data of these compounds.

In addition to the conformational behaviour as described above, another conformational aspect of the *N*-alkylated benzamides may account for their reduced dopamine D_{2A} receptor affinities. Full geometry optimization of the minimum energy rotamers of *N*,*N*-dimethylbenzamide resulted in an out-of-plane orientation of the aromatic nucleus with respect to the amide moiety of approximately 52°. Previously reported SAFIR studies on 2-aminotetralin-derived substituted benzamides have

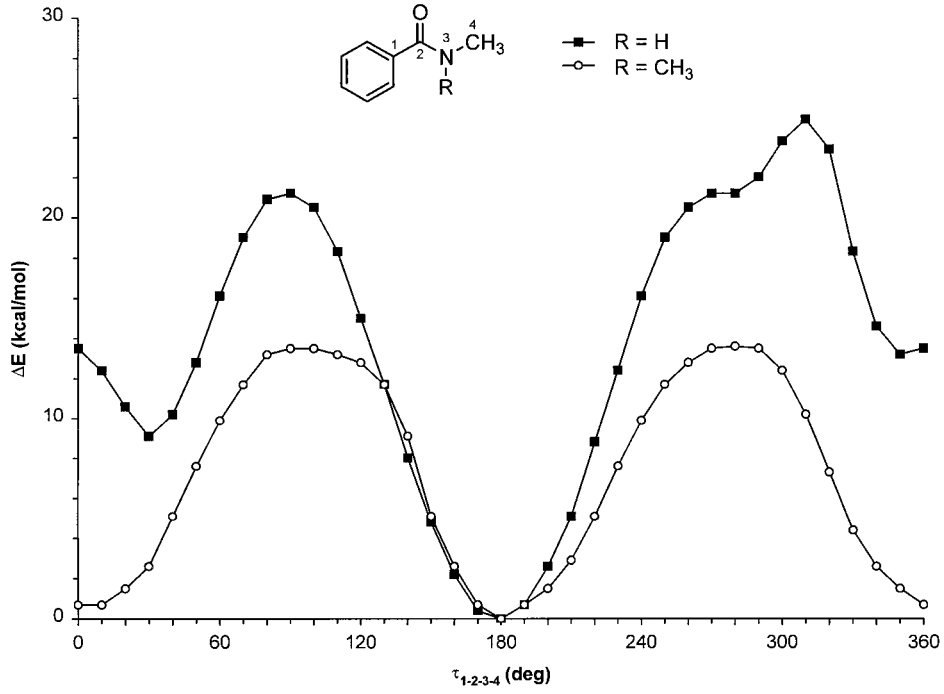


Figure 1. Rotation barriers around the amide bonds of *N*-methylbenzamide (R = H, black squares) and *N*,*N*-dimethylbenzamide (R = CH_3, open circles), as obtained from AM1 calculations.

shown that benzamides with a 2,6-dimethoxy substitution pattern have consistently lower affinities for the dopamine D_{2A} receptor than their 2,3-dimethoxy- or unsubstituted analogues, presumably because they cannot adopt a coplanar orientation of the aromatic ring and the amide function.[1] Therefore, this conformational effect of amide *N*-alkylation may also contribute to the reduced dopamine D_{2A} receptor affinities of **8–10**.

The receptor binding data of compounds **1** and **14–18** reveal that the presence of a substituent at the basic nitrogen atom with about the size of a *n*-propyl group is optimal for high affinities at all three receptor subtypes. The hydrogen- and *N*-methyl-substituted analogues **15** and **16** have somewhat lower affinities, while introduction of a second bulky substituent next to the *N*-benzamidoethyl side-chain, as in **14**, results in strong loss of affinity for both the dopamine D_{2A} and serotonin 5-HT_{1A} receptor. These structural requirements are similar to those of the DPATs[12–17] and support the previously stated hypothesis[1,2] that the 2-aminotetralin moieties of both classes of compounds may occupy the same binding sites. For the DPATs and structurally closely related compounds, these specific requirements for the nitrogen substituents have been rationalized by proposing the presence of a pocket in the dopamine D_2 receptor, capable of accommodating unbranched *N*-substituents not larger than *n*-propyl.[14,18,19] Using molecular modeling studies, Malmberg et al.[20] have shown the presence of such a pocket in both the dopamine D_2 and D_3 receptor. In view of the similarities in the SAFIR of the DPATs and the 2-aminotetralin-derived benzamides, it is likely that the *N*-alkyl substituents of **1**, **17**, and **18** protrude into this 'propyl cleft' while binding to the dopamine D_{2A} or D_3 receptor.

Chain elongation of the benzamidoethyl side-chain of **1** with one methylene group (**22**) results in about 15-fold reduction of the affinities for the dopamine D_{2A} and the serotonin 5-HT_{1A} receptor. Surprisingly, the phthalimidopropyl analogue **21**, a synthetic intermediate for the preparation of **22** which was also evaluated in the receptor binding assays, and as such the chain-elongated analogue of the inactive **5**, had affinities comparable to those of **22**. Therefore, the benzamidopropyl and phthalimidopropyl side-chains of **22** and **21** probably occupy a different accessory binding site than the analogues with a benzamidoethyl side-chain. These observations further support the previously postulated hypothesis that the benzamidoethyl side-chain of the 2-aminotetralin-derived benzamides may occupy a specific binding site in the dopamine D_2 and D_3 receptors, which may be identical to the binding site of 2-pyrrolidinylmethyl-derived substituted benzamides.[1]

Conclusions

The SAFIR of the presented compounds revealed that the aromatic ring of the benzamide moiety of 5-OMe-BPAT (**1**) contributes to the high affinities of this compound for dopamine D_2, D_3, and serotonin 5-HT_{1A} receptors, although it can be replaced by a cyclohexane ring without loss of affinity. Furthermore, **1** may interact with the dopamine D_2 and D_3 receptors through hydrogen bond formation with its carbonyl group. Investigation of the role of the amide hydrogen atom by the preparation and evaluation of amide *N*′-alkylated analogues of **1** was not conclusive, since dynamic NMR and molecular modeling studies on these compounds revealed that conformational effects of amide *N*′-alkylation may be responsible for the decreased dopaminergic affinities of these compounds. The effects of the modifications of the amide moiety on the serotonin 5-HT_{1A} receptor affinity were less pronounced, suggesting that the benzamidoethyl side-chain of **1** as a whole enhances the affinity for this receptor subtype probably not by hydrogen bond formation with its amide moiety, but through hydrophobic interactions with an accessory binding site. The structural requirements for the substituents at the basic nitrogen atom of **1** are comparable to those of the DPATs, supporting the hypothesis that the 2-aminotetralin moieties of the two classes of compounds may share the same binding sites. The benzamidoethyl side-chain of **1** probably occupies a specific binding site in the dopamine D_2 and D_3 receptors.

Experimental

Chemistry

General remarks. Unless otherwise indicated, all materials were purchased from commercial suppliers and used without further purification. All basic amine products were converted to their corresponding hydrochloride or oxalate salts by adding an equimolar amount of a 1 M ethereal HCl solution or an ethanolic solution of oxalic acid to a solution of the free base in ether. All chemical data, except for TLC analyses, were obtained on the salt forms, unless otherwise stated. TLC analyses were carried out on aluminium plates (Merck) precoated with silica gel 60 F_{254} (0.2 mm), and spots were visualised with UV light and I_2. Gravity column chromatography was performed using silica gel (Merck 60). Melting points were determined in open glass capillaries on an Electrothermal digital melting-point apparatus and are uncorrected. IR spectra (KBr pellets) were recorded on an ATI-Mattson Genesis Series FT-IR spectrophotometer, and only the important absorptions are indicated. Broad peaks (b) have been indicated as such. ^{1}H NMR spectra were recorded at 200 MHz on a Varian Gemini-200 spectrometer or at 300 MHz on a Varian VXR-300 spectrometer. ^{1}H NMR chemical shifts are denoted in δ units (ppm) relative to the solvent and converted to the TMS scale, using 7.26 for $CDCl_3$ and 3.30 for CD_3OD. The following abbreviations are used to indicate spin multiplicities: s (singlet), bs (broad singlet), d (doublet), dd (doublet of doublets), t (triplet), m (multiplet). ^{13}C NMR spectra were recorded at 50 MHz on a Varian Gemini-200 spectrometer or at 75 MHz on a Varian VXR-300 spectrometer. ^{13}C NMR chemical shifts are denoted in δ units (ppm) relative to the solvent and converted to the TMS scale, using 76.91 for $CDCl_3$ and 49.50 for CD_3OD. Dynamic ^{1}H and ^{13}C NMR experiments were performed on a Varian Unity

Plus 500 MHz NMR spectrometer. Chemical ionisation mass spectra were recorded on a NERMAG R 3010 triple quadrupole mass spectrometer equipped with a home-built atmospheric pressure ionisation source and ionspray interface. Alternatively, chemical ionization mass spectra were recorded on a Unicam Automass mass spectrometer. Ammonia was used as the reactant gas and samples were introduced into the ion source by means of the direct insertion probe. Elemental analyses (C, H, and N) for target compounds were performed at the Micro Analytical Department, University of Groningen, and unless otherwise indicated, the obtained results were within 0.4% of the theoretical values.

5-Methoxy-2-[*N*-(2-acetamidoethyl)-*N*-*n*-propylamino]-tetralin hydrochloride (3). Acetic anhydride (0.90 mL, 9.5 mmol) was added dropwise at room temperature to a firmly stirred mixture of **2**·$(HCl)_2$[1] (0.50 g, 1.5 mmol), NaOAc (0.70 g, 0.9 mmol), EtOAc (16 mL) and H_2O (5 mL). After stirring overnight at room temperature, the reaction mixture was diluted with H_2O (10 mL), the phases were separated and the H_2O layer was extracted with EtOAc (2×15 mL). Subsequently the EtOAc layers were combined and washed with saturated aqueous solutions of $NaHCO_3$ (3×20 mL) and NaCl (20 mL) and finally dried over Na_2SO_4. Evaporation of the solvent under reduced pressure gave the crude acetamide as a brown oil. Purification by silica column chromatography [eluent: MeOH/CH_2Cl_2, 1/15 (v/v)] yielded 0.29 g (1.0 mmol, 64%) of the pure base of **3** as a colourless oil: mp 56–58 °C; IR: cm^{-1} 3421 (b), 3246 (b), 3059, 2940, 2837, 2627 (b), 1670, 1588, 1543; ^1H NMR (base, 200 MHz, $CDCl_3$): δ 0.89 (t, J = 7.3 Hz, 3H), 1.36–1.66 (m, 3H), 1. 96 (s, 3H), 2.45–2.77 (m, 7H), 2.85–3.04 (m, 2H), 3.22–3.29 (m, 2H), 3.79 (s, 3H), 6.30 (bs, 1H), 6.66 (dd, J = 8.7 Hz, 8.7 Hz, 2H), 7.06 (t, J = 7.8 Hz, 1H); ^{13}C NMR (base, 50 MHz, $CDCl_3$): δ 11.5, 21.6, 23.0, 23.5, 25.2, 31.8, 37.5, 48.4, 51.9, 55.0, 55.7, 106.8, 121.4, 124.9, 126.1, 137.4, 157.1, 169.9; MS (CI with NH_3): m/z (rel. intensity) 161 (28), 202 (11), 232 (48), 275(13), 305 (100, M + 1); Anal. calcd for $C_{18}H_{28}N_2O_2$·HCl·H_2O: C 60.23, H 8.72, N 7.81; obsd C 60.14, H 8.90, N 7.89.

5-Methoxy-2-[*N*-(2-cyclohexylcarboxamidoethyl)-*N*-*n*-propylamino]tetralin hydrochloride (4). A solution of cyclohexylcarboxylic acid chloride (0.55 g, 3.8 mmol) in CH_2Cl_2 (10 mL) was added dropwise to a firmly stirred, ice-cooled mixture of **2**·$(HCl)_2$ (0.50 g, 1.5 mmol), 10% aqueous NaOH solution (12 mL) and CH_2Cl_2 (50 mL). When addition was complete, the reaction mixture was allowed to warm to room temperature and stirring was continued overnight. The reaction mixture was poured into H_2O (50 mL), the phases were separated, and the aqueous phase was extracted with CH_2Cl_2 (2×50 mL) The organic layers were combined and subsequently washed with saturated aqueous $NaHCO_3$ solution (3×50 mL), H_2O (50 mL) and brine (50 mL). After drying (Na_2SO_4) and filtration, the solvent was evaporated, which gave the crude amide as an orange oil. Purification by silica column chromatography [eluent: MeOH/CH_2Cl_2, 1/15 (v/v)] yielded 0.26 g (0.7 mmol, 47%) of the pure base of **4** as a colourless oil: mp 60–62 °C; IR: cm^{-1}; ^1H NMR (base, 200 MHz, $CDCl_3$): δ 0.91 (t, J = 7.3 Hz, 3H), 1.18–2.15 (m, 16H), 2.44–3.06 (m, 8H), 3.23–3.33 (m, 2H), 3.80 (s, 3H), 6.32 (bs, 1H), 6.67 (dd, J = 8.0 Hz, 8.2 Hz, 2H), 7.09 (t, J = 8.1 Hz, 1H); ^{13}C NMR (base, 50 MHz, $CDCl_3$): δ 11.8, 21.9, 23.7, 25.4, 25.8, 29.7, 32.1, 37.2, 45.5, 48.7, 52.2, 55.2, 55.9, 107.0, 121.5, 125.0, 126.2, 137.4, 157.2, 175.9; MS (CI with NH_3): m/z (rel. intensity) 161 (7), 232 (48), 373 (100, M + 1); Anal. calcd for $C_{23}H_{36}N_2O_2$·HCl·1/2H_2O: C 66.07, H 9.18, N 6.70; obsd C 65.95, H 9.30, N 6.62.

5-Methoxy-2-[*N*-(2-phthalimidoethyl)-*N*-*n*-propylamino]-tetralin hydrochloride (5). A suspension of phthalic anhydride (0.25 g, 1.7 mmol), NaOAc (0.50 g, 6.1 mmol) and **2**·$(HCl)_2$ (0.25 g, 0.7 mmol) in glacial acetic acid (5 mL) was refluxed under a nitrogen atmosphere for 30 min. After cooling, saturated aqueous $NaHCO_3$ solution (25 mL) and $CHCl_3$ (25 mL) were added, stirring was continued for a few minutes and then the phases were separated. The organic layer was washed with saturated aqueous $NaHCO_3$ solution (4×25 mL), the aqueous layers were collected and washed with $CHCl_3$ (2×25 mL). The collected $CHCl_3$ layers were subsequently washed with H_2O (25 mL), brine (25 mL) and then dried over Na_2SO_4. After filtration and evaporation of the solvent, the crude phthalimide was afforded as a brown oil. Purification by silica column chromatography [eluent: MeOH/CH_2Cl_2, 1/50 (v/v)] yielded 0.15 g (0.4 mmol, 51%) of the pure base of **5** as a light yellow oil: mp 228–230 °C dec; IR: cm^{-1} 3461 (b), 2943, 2881, 2842, 2362 (b), 1771, 1709, 1590; ^1H NMR (base, 200 MHz, $CDCl_3$): δ 0.82 (t, J = 7.3 Hz, 3H), 1.33–1.62 (m, 3H), 1.92–2.02 (m, 1H), 2.42–3.03 (m, 9H), 3.70–3.79 (m, 5H), 6.64 (dd, J = 7.6 Hz, 7.6 Hz, 2H), 7.06 (t, J = 7.8 Hz, 1H), 7.68–7.74 (m, 2H), 7.79–7.86 (m, 2H); ^{13}C NMR (base, 50 MHz, $CDCl_3$): δ 11.4, 21.8, 23.6, 25.6, 31.8, 37.4, 47.7, 52.6, 55.0, 56.0, 106.7, 121.5, 122.9, 125.0, 125.9, 132.1, 133.6, 137.8, 157.1, 168.3; MS (CI with NH_3): m/z (rel. intensity) 161 (2), 232 (4), 393 (100, M + 1); Anal. calcd for $C_{24}H_{28}N_2O_3$·HCl·1/4H_2O: C 66.49, H 6.87, N 6.46; obsd C 66.67, H 6.86, N 6.38.

5-Methoxy-2-[*N*-(2-benzenesulfonamidoethyl)-*N*-*n*-propylamino]tetralin (6). Benzenesulfonyl chloride (0.29 g, 1.6 mmol) was added dropwise at 0 °C to a vigorously stirred mixture of **2**·$(HCl)_2$ (0.50 g, 1.5 mmol), K_2CO_3 (0.41 g, 3.0 mmol), $CHCl_3$ (50 mL) and H_2O (40 mL). The mixture was stirred at room temperature for 1 h and then the phases were separated. The organic layer was washed with H_2O (2×50 mL), dried (Na_2SO_4) and filtered. The filtrate was concentrated under reduced pressure to give the crude sulfonamide as a brown oil. Purification using silica column chromatography [eluent: MeOH/CH_2Cl_2, 1/15 (v/v)] yielded 0.51 g (1.3 mmol, 85%) of the pure base of **6** as a colourless oil: mp 104–106 °C; IR: cm^{-1} 3422, 3065, 2939, 2881, 2837, 2600 (b), 2487 (b), 1588, 1329, 1160; ^1H NMR (base, 200 MHz, $CDCl_3$): δ 0.76 (t, J = 7.3 Hz, 3H), 1.19–1.48 (m, 3H), 1.83–1.91 (m, 1H), 2.24–2.75 (m, 8H), 2.88–2.99 (m, 3H), 3.78 (s, 3H), 5.27 (bs, 1H), 6.65 (dd, J = 7.9 Hz, 3.6 Hz, 2H), 7.07 (t, J = 7.9 Hz, 1H), 7.42–7.57 (m, 3H), 7.85–7.90 (m, 2H); ^{13}C NMR (base, 50 MHz, $CDCl_3$): δ 11.7, 22.0, 23.7, 25.2, 31.9, 40.9, 48.2, 51.9, 55.2, 55.7, 107.0, 121.5, 124.8, 126.3, 127.0,

129.0, 132.6, 137.4, 139.5, 157.2; MS (CI with NH_3): *m/z* (rel. intensity) 148 (21), 186 (56), 220 (33), 263 (33), 305 (17), 353 (27), 403 (100, M + 1); Anal. calcd for $C_{22}H_{30}N_2SO_3 \cdot HCl \cdot 1/4H_2O$: C 59.57, H 7.17, N 6.32; obsd C 59.48, H 7.32, N 6.26.

5-Methoxy-2-[*N*-(2-benzylaminoethyl)-*N*-*n*-propylamino]-tetralin dihydrochloride (7). A solution of **1**[1] (0.50 g, 1.4 mmol) in dry THF (75 mL) was added dropwise to a stirred suspension of $LiAlH_4$ (2.00 g) in dry THF (75 mL). After refluxing under a nitrogen atmosphere overnight, the reaction mixture was cooled to room temperature and excess $LiAlH_4$ was decomposed by subsequent careful addition of H_2O (2 mL), 4N aqueous NaOH solution (2 mL) and H_2O (6 mL).The precipitate was removed by filtration and the filtrate was concentrated in vacuo. The resulting oil was taken up in CH_2Cl_2 (100 mL) and the solution was dried over Na_2SO_4. After filtration and evaporation of the solvent, the crude product was purified using silica column chromatography (eluent: CH_2Cl_2), which gave 0.34 g (1.0 mmol, 71%) of the pure base of **7** as a colourless oil: mp 120–121 °C; IR: cm^{-1} 3404 (b), 2938, 2837, 2619 (b), 1588; ^1H NMR (base, 200 MHz, $CDCl_3$): δ 0.89 (t, $J = 7.3$ Hz, 3H), 1.41–1.63 (m, 3H), 1.99–2.03 (m, 1H), 2.45–3.08 (m, 12H), 3.83 (s, 3H), 3.85 (s, 2H), 6.70 (dd, $J = 11.8$ Hz, 7.9 Hz, 2H), 7.11 (t, $J = 7.9$ Hz, 1H), 7.25–7.37 (m, 5H); ^{13}C NMR (base, 50 MHz, $CDCl_3$): δ 11.8, 22.2, 23.9, 25.5, 32.1, 47.5, 49.6, 52.5, 53.9, 55.2, 56.1, 106.9, 121.6, 125.2, 126.1, 126.9, 128.1, 128.4, 138.0, 140.1, 157.2; MS (CI with NH_3): *m/z* (rel. intensity) 72 (41), 161 (90), 232 (100), 353 (2, M + 1); Anal. calcd for $C_{23}H_{32}N_2O \cdot (HCl)_2 \cdot 1/4H_2O$: C 64.24, H 8.10, N 6.52; obsd C 64.23, H 8.62, N 6.48.

5-Methoxy-2-{*N*-[2-(*N'*-methyl)benzamidoethyl]-*N*-*n*-propylamino}tetralin hydrochloride (8). Powdered KOH (0.36 g, 6.4 mmol) was added to DMSO (2 mL) and the suspension was stirred for 5 min. Then a solution of **1**[1] (0.57 g, 1.6 mmol) in DMSO (1 mL) was added, immediately followed by CH_3I (0.45 g, 3.2 mmol). Stirring was continued overnight at room temperature, after which the reaction mixture was poured into H_2O (20 mL) and extracted with CH_2Cl_2 (3×20 mL). After subsequent washing with saturated aqueous $NaHCO_3$ solution (3×10 mL), H_2O (10 mL), and brine (10 mL), the organic layer was dried (Na_2SO_4) and filtered. After evaporation of the solvent, the residue was purified by silica column chromatography [eluent: $MeOH/CH_2Cl_2$, 1/20 (v/v)], which yielded 0.46 g (1.2 mmol, 75%) of the pure base of **8** as a colourless oil: mp 91–93 °C; IR: cm^{-1} 3416 (b), 2937, 2836, 2452 (b), 1630, 1588; ^1H NMR (base, 500 MHz, $C_2D_4Cl_2$, 95 °C): δ 0.90 (as, 3H), 1.44–1.67 (m, 3H), 2.02–2.09 (m, 1H), 2.48–3.03 (m, 7H), 3.07 (s, 3H), 3.46–3.58 (m, 2H), 3.83 (s, 3H), 6.69 (dd, $J = 13.5$ Hz, 7.9 Hz, 2H), 7.09 (t, $J = 7.9$ Hz, 1H), 7.37–7.45 (m, 5H); ^{13}C NMR (base, 125 MHz, $C_2D_4Cl_2$, 95 °C): δ 13.7, 23.8, 25.4, 27.4, 33.8, 50.3, 55.3, 57.5, 60.2, 110.0, 123.6, 126.8, 128.5, 128.9, 130.4, 131.5, 138.6, 159.4, 173.6; MS (CI with NH_3): *m/z* (rel. intensity) 69 (28), 153 (80), 220 (100), 247 (22), 381 (7, M + 1); Anal. calcd for $C_{24}H_{32}N_2O_2 \cdot HCl \cdot 1/2H_2O$: C 67.65, H 8.06, N 6.58; obsd C 67.68, H 8.19, N 6.50.

5-Methoxy-2-{*N*-[2-(*N'*-ethyl)benzamidoethyl]-*N*-*n*-propylamino}tetralin hydrochloride (9). This compound was essentially prepared as described for **8**, using ethyl iodide instead of CH_3I. Yield 59%; mp 96–98 °C; IR: cm^{-1} 3421 (b), 2966, 2880, 2836, 2457, 1628, 1588; ^1H NMR (base, 500 MHz, $C_2D_4Cl_2$, 95 °C): δ 0.88 (as, 3H), 1.18 (as, 3H), 1.30–1.55 (m, 3H), 2.01–2.07 (m, 1H), 2.53–3.01 (m, 9H), 3.44–3.50 (m, 4H), 3.82 (s, 3H), 6.68 (dd, $J = 16.1$ Hz, 7.6 Hz, 2H), 7.09 (t, $J = 6.0$ Hz, 1H), 7.37–7.42 (m, 5H); MS (CI with NH_3): *m/z* (rel. intensity) 69 (31), 112 (20), 150 (44), 220 (51), 395 (100, M + 1); Anal. calcd for $C_{25}H_{34}N_2O_2 \cdot HCl \cdot 1/2H_2O$: C 68.23, H 8.26, N 6.37; obsd C 68.15, H 8.38, N 6.28.

5-Methoxy-2-{*N*-[2-(*N'*-*n*-propyl)benzamidoethyl]-*N*-*n*-propylamino}tetralin hydrochloride (10). This compound was essentially prepared as described for **8**, using *n*-propyl iodide instead of CH_3I. Yield 42%; mp 118–120 °C; IR: cm^{-1}; ^1H NMR (base, 500 MHz, $C_2D_4Cl_2$, 95 °C): δ 0.88 (as, 6H), 1.34–1.75 (m, 6H), 1.96–2.10 (m, 1H), 2.37–3.12 (m, 8H), 3.27–3.58 (m, 4H), 3.82 (s, 3H), 6.66–6.69 (m, 2H), 7.09 (t, $J = 7.9$ Hz, 1H), 7.37–7.44 (m, 5H); MS (CI with NH_3): *m/z* (rel. intensity) 164 (14), 367 (6), 409 (100, M + 1); Anal. calcd for $C_{26}H_{36}N_2O_2 \cdot HCl \cdot 1/2H_2O$: C 68.76, H 8.45, N 6.17; obsd C 68.71, H 8.51, N 6.08.

5-Methoxy-2-(*N*-cyanomethyl-*N*-benzylamino)tetralin hydrochloride (12). Bromoacetonitrile (2.44 g, 20.34 mmol) was added to a mixture of **11**·HCl[9] (2.47 g, 8.1 mmol), K_2CO_3 (2.81 g, 20.3 mmol) and KI (0.34 g, 2.1 mmol) in acetone (100 mL). After refluxing overnight, the reaction mixture was cooled and the solids were removed by filtration.The filtrate was concentrated and the resulting oil was purified by silica column chromatography (eluent: CH_2Cl_2), yielding 2.00 g (6.5 mmol, 80%) of the pure base of **12** as a light yellow oil: mp 173–175 °C (EtOH); IR: cm^{-1} 2985, 2928, 2889, 2829, 2262 (b), 1601, 1587; ^1H NMR (base, 200 MHz, $CDCl_3$): δ 1.72–1.91 (m, 1H), 2.30–2.36 (m, 1H), 2.61–2.78 (m, 1H), 2.89–3.18 (m, 4H), 3.52 (s, 2H), 3.84–4.00 (m, 2H), 3.88 (s, 2H), 6.79 (dd, $J = 12.0$ Hz, 7.8 Hz, 2H), 7.20 (t, $J = 7.8$ Hz, 1H), 7.32–7.46 (m, 5H); ^{13}C NMR (base, 50 MHz, $CDCl_3$): δ 22.7, 26.4, 33.3, 38.2, 54.1, 55.1, 57.5, 107.2, 116.5, 121.4, 126.4, 127.6, 128.6, 128.8, 136.2, 137.8, 157.1; MS (CI with AcOH): *m/z* 307 (M + 1).

5-Methoxy-2-[*N*-(2-aminoethyl)-*N*-benzylamino]tetralin oxalate (13). A suspension of **12** (1.50 g, 4.4 mmol) and $LiAlH_4$ (2.00 g) in dry THF (100 mL) was refluxed overnight under a nitrogen atmosphere. After cooling to room temperature, excess $LiAlH_4$ was decomposed as described for **7**. The precipitate was removed by filtration and the filtrate was dried over Na_2SO_4. After filtration and evaporation of the solvent, 1.29 g (4.2 mmol, 95%) of the pure base of **13** was obtained as a colourless oil: mp 120–121 °C (EtOH); IR: cm^{-1} 3413 (b), 2937 (b), 2837, 2534 (b), 1719, 1589; ^1H NMR (base, 200 MHz, $CDCl_3$): δ 1.60–1.74 (m, 1H), 1.95 (bs, 2H), 2.13–2.20 (m, 1H), 2.46–2.77 (m, 5H), 2.86–3.14 (m, 4H), 3.75 (s, 2H), 3.82 (s, 3H), 6.72 (dd, $J = 18.8$ Hz, 7.8 Hz, 2H), 7.13 (t, $J = 7.9$ Hz, 1H), 7.28–7.44 (m, 5H); ^{13}C NMR

(base, 50 MHz, $CDCl_3$): δ 23.7, 24.8, 31.9, 40.0, 52.6, 54.6, 55.0, 55.6, 106.8, 121.5, 125.1, 126.1, 126.7, 128.2, 128.4, 137.8, 140.8, 157.2; MS (CI with AcOH): *m/z* 311 (M + 1).

5-Methoxy-2-[*N*-(2-benzamidoethyl)-*N*-benzylamino]tetralin hydrochloride (14). This compound was essentially prepared as described for **4**, starting from **13**. Yield 53%; mp 112–114 °C; IR: cm^{-1} 3261 (b), 2941, 2835, 2489 (b), 1655, 1588, 1535; ^1H NMR (base, 200 MHz, $CDCl_3$): δ 1.64–1.72 (m, 1H), 2.18–2.23 (m, 1H), 2.50–2.64 (m, 1H), 2.87–2.96 (m, 4H), 3.05–3.16 (m, 2H), 3.48–3.54 (m, 2H), 3.71–3.87 (m, 5H), 6.73 (dd, *J* = 13.7 Hz, 7.7 Hz, 2H), 7.04–7.09 (m, 1H), 7.15 (t, *J* = 7.7 Hz, 1H), 7.23–7.57 (m, 8H), 7.79 (dd, *J* = 8.1 Hz, 1.7 Hz, 2H); ^{13}C NMR (base, 50 MHz, $CDCl_3$): δ 23.8, 25.1, 32.1, 38.0, 48.1, 54.6, 55.2, 56.1, 107.1, 121.6, 125.0, 126.4, 127.0, 127.3, 128.5, 128.6, 128.8, 131.3, 134.7, 137.3, 140.0, 157.2, 167.3; MS (CI with NH_3): *m/z* (rel. intensity) 106 (21), 139 (20), 174 (32), 206 (78), 280 (14), 325 (28), 415 (100, M + 1); Anal. calcd for $C_{27}H_{30}N_2O_2 \cdot HCl \cdot 3/4H_2O$: C 69.80, H 7.07, N 6.03; obsd C 69.95, H 7.09, N 6.11.

5-Methoxy-2-[*N*-(2-benzamidoethyl)amino]tetralin oxalate (15). A solution of the free base of **14** (0.56 g, 1.4 mmol) in absolute EtOH (50 mL) was transferred to a Parr flask, 10% Pd-on-C catalyst (0.30 g) was added and the solution was hydrogenated overnight under 4 atm H_2 at room temperature. The catalyst was removed by filtration and the solvent was evaporated, yielding 0.36 g (1.1 mmol, 82%) of the pure base of **15** as a colourless oil: mp 208–210 °C dec (MeOH); IR: cm^{-1} 3281 (b), 3045, 2936, 2836, 2505, 1735, 1632, 1562; ^1H NMR (base, 200 MHz, $CDCl_3$): δ 1.55–1.70 (m, 2H), 2.00–2.09 (m, 1H), 2.51–2.67 (m, 2H), 2.81–3.06 (m, 5H), 3.50–3.58 (m, 2H), 3.81 (s, 3H), 6.68 (dd, *J* = 7.8 Hz, 4.2 Hz, 2H), 6.96 (bs, 1H), 7.10 (t, *J* = 7.9 Hz, 1H), 7.36–7.53 (m, 3H), 7.53–7.79 (m, 2H); ^{13}C NMR (base, 50 MHz, $CDCl_3$): δ 21.4, 28.8, 36.4, 39.8, 45.4, 52.4, 55.0, 106.9, 121.4, 124.8, 126.1, 126.8, 128.4, 131.2, 134.5, 136.2, 157.0, 167.4; MS (CI with AcOH): *m/z* 325 (M + 1); Anal. calcd for $C_{20}H_{24}N_2O_2 \cdot C_2H_2O_4$: C 63.74, H 6.34, N 6.76; obsd C 63.59, H 6.36, N 6.76.

5-Methoxy-2-[*N*-(2-benzamidoethyl)-*N*-methylamino]tetralin oxalate (16). A solution of **15** (0.10 g, 0.3 mmol) in MeOH (50 mL) was transferred to a Parr flask, 37% aqueous formaldehyde solution (5 mL) and 10% Pd-on-C catalyst (0.10 g) were added, and the reaction mixture was hydrogenated overnight under 4 atm H_2 at 55 °C. The catalyst was removed by filtration and the filtrate was concentrated. The residue was dissolved in CH_2Cl_2 and subsequently washed with 10% aqueous $NaHCO_3$ solution, H_2O and brine. After drying (Na_2SO_4) and filtering, the solvent was evaporated, which gave the crude product as a yellow oil. Purification by silica column chromatography [eluent: MeOH/CH_2Cl_2, 1/20 (v/v)] yielded 80 mg (0.24 mmol, 77%) of the pure base of **16** as a colourless oil: mp 141–143 °C; IR: cm^{-1} 3395 (b), 3065, 2949, 2837, 1719, 1654, 1588, 1542; ^1H NMR (base, 200 MHz, $CDCl_3$): δ 1.62–1.73 (m, 1H), 2.03–2.09 (m, 1H), 2.37 (s, 3H), 2.47–2.64 (m, 1H), 2.74–3.05 (m, 6H), 3.51–3.59 (m, 2H), 3.81 (s, 3H), 6.69 (dd, *J* = 7.3 Hz, 7.3 Hz, 2H), 7.00 (bs, 1H), 7.10 (t, *J* = 7.8 Hz, 1H), 7.38–7.54 (m, 3H), 7.76 (d, *J* = 8.1 Hz, 2H); ^{13}C NMR (base, 50 MHz, $CDCl_3$): δ 23.0, 25.4, 31.5, 36.9, 51.4, 55.0, 59.2, 106.9, 121.4, 124.9, 126.2, 126.8, 131.1, 134.6, 136.9, 157.1, 167.3; MS (CI with AcOH): *m/z* 325 (M + 1); Anal. calcd for $C_{21}H_{26}N_2O_2 \cdot C_2H_2O_4 \cdot 1/4H_2O$: C 63.79, H 6.65, N 6.47; obsd C 63.46, H 6.75, N 6.57.

5-Methoxy-2-[*N*-(2-benzamidoethyl)-*N*-ethylamino]tetralin hydrochloride (17). This compound was prepared essentially as described for **16**, using acetaldehyde instead of formaldehyde. Yield 88%; mp 104–105 °C; IR: cm^{-1} 3422 (b), 3271 (b), 2938, 2836, 2617 (b), 2472 (b), 2357, 1649, 1588, 1534; ^1H NMR (base, 200 MHz, $CDCl_3$): δ 1.12 (t, *J* = 7.3 Hz, 3H), 1.24–1.73 (m, 1H), 2.02–2.17 (m, 1H), 2.47–3.07 (m, 9H), 3.40–3.60 (m, 2H), 3.81 (s, 3H), 6.68 (t, *J* = 7.3 Hz, 2H), 7.10 (t, *J* = 8.1 Hz, 1H), 7.18 (bs, 1H), 7.39–7.54 (m, 3H), 7.80–7.85 (m, 2H); ^{13}C NMR (base, 50 MHz, $CDCl_3$): δ 14.1, 23.6, 25.7, 32.3, 38.1, 44.1, 480, 55.2, 55.8, 107.0, 121.5, 125.0, 126.3, 126.9, 128.5, 131.2, 134.7, 137.4, 157.2, 167.2; MS (CI with NH_3): *m/z* (rel. intensity) 161 (14), 193 (20), 218 (57), 305 (7), 353 (100, M + 1); Anal. calcd for $C_{22}H_{28}N_2O_2 \cdot HCl \cdot 1/4H_2O$: C 67.15, H 7.57, N 7.12; obsd C 67.43, H 7.92, N 7.17.

5-Methoxy-2-[*N*-(2-benzamidoethyl)-*N*-allylamino]tetralin hydrochloride (18). Allyl bromide (0.10 g, 0.8 mmol) was added to a stirred suspension of **15** (0.10 g, 0.2 mmol), Cs_2CO_3 (0.23 g, 0.7 mmol) and a catalytic amount of KI in MeCN (50 mL). The reaction mixture was refluxed overnight, cooled to room temperature and then the solids were removed by filtration.The filtrate was concentrated in vacuo, which gave the crude tertiary amine as a yellow oil. Purification by silica column chromatography [eluent: MeOH/CH_2Cl_2, 1/20 (v/v)] gave the pure base of **18** as a colourless oil. Yield 32 mg (0.1 mmol, 36%); mp 100–102 °C; IR: cm^{-1} 3331 (b), 3065, 2930, 2836, 1633, 1601, 1584; ^1H NMR (base, 300 MHz, $CDCl_3$): δ 1.56–1.70 (m, 1H), 2.03–2.08 (m, 1H), 2.48–2.60 (m, 1H), 2.75–2.90 (m, 4H), 2.96–3.09 (m, 2H), 3.28 (d, *J* = 6.2 Hz, 2H), 3.44–3.57 (m, 2H), 3.80 (s, 3H), 5.12 (d, *J* = 9.9 Hz, 1H), 5.23 (d, *J* = 17.0 Hz, 1H), 5.80–5.93 (m, 1H), 6.67 (t, *J* = 8.4 Hz, 2H), 6.90 (bs, 1H), 7.09 (t, *J* = 7.9 Hz, 1H), 7.42–7.53 (m, 3H), 7.77 (d, *J* = 8.1 Hz, 2H); ^{13}C NMR (base, 75 MHz, $CDCl_3$): δ 23.8, 25.8, 32.5, 37.9, 48.1, 53.6, 55.4, 56.2, 107.2, 117.4, 121.7, 125.1, 126.5, 127.0, 128.8, 131.5, 135.0, 136.9, 137.5, 157.4, 167.4; MS (CI with NH_3): *m/z* (rel. intensity) 77 (33), 105 (53), 161 (79), 203 (32), 230 (100), 324 (2), 365 (3, M + 1); Anal. calcd for $C_{23}H_{28}N_2O_2 \cdot HCl \cdot 1/2H_2O$: C 67.37, H 7.39, N 6.83; obsd C 67.16, H 7.77, N 6.75.

5-Methoxy-2-[*N*-(3-phthalimidopropyl)-*N*-*n*-propylamino]-tetralin oxalate (20). A stirred suspension of *N*-(3-bromopropyl)phthalimide (3.14 g, 11.7 mmol), K_2CO_3 (1.62 g, 11.7 mmol), KI (0.13 g, 0.78 mmol) and **19**·HCl[10] (1.00 g, 3.9 mmol) in MeCN (150 mL) was refluxed for 24 h. After cooling, the reaction mixture was filtered and the MeCN was evaporated from the

filtrate. The crude product was purified by silica column chromatography [eluent: EtOAc/petroleum ether (bp 40–60), 1/3 (v/v)], which yielded 1.16 g (2.9 mmol, 74%) of the pure base of **20** as a colourless oil: mp 157–159 °C; IR: cm^{-1} 2980, 2943, 2836, 2669 (b), 1768, 1698, 1591; ^1H NMR (base, 200 MHz, $CDCl_3$): δ 0.90 (t, $J=7.3$ Hz, 3H), 1.41–1.56 (m, 3H), 1.76–1.90 (m, 2H), 1.94–2.07 (m, 1H), 2.47 (dd, $J=8.2$ Hz, 6.5 Hz, 2H), 2.61 (t, $J=7.1$ Hz, 2H), 2.76–3.03 (m, 5H), 3.71–3.78 (m, 5H), 6.65 (dd, $J=10.1$ Hz, 8.0 Hz, 2H), 7.05 (t, $J=7.9$ Hz, 1H), 7.66–7.70 (m, 2H), 7.79–7.84 (m, 2H); ^{13}C NMR (base, 50 MHz, $CDCl_3$): δ 11.9, 22.2, 23.9, 25.5, 27.9, 31.9, 36.5, 47.9, 52.3, 55.1, 56.2, 106.8, 121.6, 123.0, 125.2, 126.1, 132.2, 133.8, 138.0, 157.2, 168.3; MS (CI with NH_3): m/z 407 (M + 1); Anal. calcd for $C_{25}H_{30}N_2O_3 \cdot C_2H_2O_4$: C 65.30, H 6.51, N 5.64; obsd C 65.29, H 6.43, N 5.34.

5-Methoxy-2-[*N*-(3-aminopropyl)-*N*-*n*-propylamino]tetralin oxalate (21). Hydrazine hydrate (10 mL) was added slowly to a stirred solution of **20** (0.90 g, 2.2 mmol) in absolute EtOH (50 mL). The reaction mixture was stirred for 1 h at room temperature and then the EtOH was removed in vacuo. The resulting oil was taken up in EtOAc and the solution was washed with a saturated aqueous K_2CO_3 solution. The H_2O layer was extracted with EtOAc (2×25 mL), the organic layers were combined and subsequently washed with H_2O (25 mL) and brine (25 mL). After drying over Na_2SO_4, the organic layer was filtered and evaporated, yielding 0.48 g (1.7 mmol, 79%) of the pure base of **21** as a colourless oil: mp 136–138 °C (EtOH); IR: cm^{-1} 3412 (b), 2965, 2837, 2762, 2640, 2538, 2120 (b), 1592, 1518; ^1H NMR (base, 200 MHz, $CDCl_3$): δ 0.89 (t, $J=7.3$ Hz, 3H), 1.38–1.67 (m, 8H), 1.98–2.08 (m, 1H), 2.43–3.06 (m, 10H), 3.79 (s, 3H), 6.67 (dd, $J=13.0$ Hz, 7.9 Hz, 2H), 7.08 (t, $J=7.9$ Hz, 1H); ^{13}C NMR (base, 50 MHz, $CDCl_3$): δ 11.9, 22.1, 23.9, 25.4, 32.0, 32.5, 40.8, 48.2, 52.3, 55.2, 56.0, 106.8, 121.6, 125.3, 126.1, 138.1, 157.2; MS (CI with AcOH): m/z 277 (M + 1).

5-Methoxy-2-[*N*-(3-benzamidopropyl)-*N*-*n*-propylamino]-tetralin hydrochloride (22). This compound was prepared as described for **4**, starting from **21**. Yield 63%; mp 62–63 °C; IR: cm^{-1} 3408 (b), 3264 (b), 3057, 2937, 2836, 2620, 2494, 1647, 1588, 1541; ^1H NMR (base, 200 MHz, $CDCl_3$): δ 0.90 (t, $J=7.3$ Hz, 3H), 1.49–1.63 (m, 3H), 1.75–1.87 (m, 2H), 2.03–2.11 (m, 1H), 2.50–2.59 (m, 3H), 2.75–2.81 (m, 4H), 2.93–3.08 (m, 2H), 3.53–3.65 (m, 2H), 3.79 (s, 3H), 6.63 (dd, $J=7.2$ Hz, 6.5 Hz, 2H), 7.08 (t, $J=7.9$ Hz, 1H), 7.37–7.49 (m, 3H), 7.80–7.84 (m, 2H), 8.34 (bs, 1H); ^{13}C NMR (base, 50 MHz, $CDCl_3$): δ 12.0, 21.5, 23.7, 24.7, 25.99, 31.7, 40.6, 49.9, 52.3, 55.2, 56.1, 107.0, 121.5, 124.9, 126.3, 127.0, 128.4, 131.1, 134.9, 137.2, 157.2, 167.4; MS (CI with NH_3): m/z (rel. intensity) 220 (11), 381 (100, M + 1); Anal. calcd for $C_{24}H_{32}N_2O_2 \cdot HCl \cdot 3/4H_2O$: C 66.95, H 8.07, N 6.51; obsd C 67.28, H 8.43, N 6.56.

Pharmacology

[^{3}H]-Raclopride binding to cloned dopamine D_{2A} and D_3 receptors, [^{3}H]-8-OH-DPAT binding to serotonin 5-HT_{1A} receptors, and **data analysis** were performed essentially as described in ref. 1.

Molecular modeling

Calculations were performed on a Silicon Graphics Indy Workstation running IRIX 5.3. *N*-methyl- and *N*,*N*-dimethylbenzamide were built in the molecular modeling package SYBYL 6.3[21] from standard fragments using the sketch mode. After minimising the starting structures within the Tripos force field with default options selected, rotamers were generated by stepwise rotating the amide bonds with a resolution of 10°. The energies of the resulting rotamers were then calculated semi-empirically with the AM1 method[11] as implemented in MOPAC 5.0 and accessed through SYBYL, applying the additional keywords 1SCF and MMOK(0).

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